



ORIGINAL ARTICLE / Cardiovascular imaging

Accuracy of multi-detector computed tomographic angiography assisted by post-processing software for diagnosis atheromatous renal artery stenosis

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KEYWORDS

Renal artery stenosis;
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Arteriography;
Accuracy

Abstract

Purpose: To compare the diagnostic performance of MDCTA versus renal angiography in the detection of > 50% renal artery stenosis in patients suspected of reno-vascular hypertension.

Materials and methods: Between January 2005 and January 2010, 92 MDCTA and renal arteriographies were retrospectively analysed. Renal angiographies were read by one interventional radiologist. Three blinded independent readers (two senior radiologists and one technician) scored MDCTA images using three different approaches. Reader 1 scored stenosis using only MPR and MIP. Reader 2 (technician) used only proprietary automatic arterial segmentation software. Reader 3 used the cited software, using manual diameter measurements.

Results: A total of 92 patients, (235 renal arteries) were assessed in which 48 significant stenosis were found by arteriography. Sensitivity, specificity, of MDCTA compared to renal arteriography were respectively per patient for reader 1: (88%; 80%); for reader 2: (58%; 80%); for reader 3: (96%; 90%) ($P < .02$).

Conclusion: When using automated vessel analysis software edited by a radiologist, MDCTA studies had a Sensibility/Specificity of 96%/90% to detect > 50% renal artery stenosis.

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Abbreviations: RAS, Renal artery stenosis; HT, Hypertension; DSA, Digital subtraction angiography; MDCTA, Multi-detector CTA; EPR, Electronic patient record; LR, Likelihood ratios; CI, Confidence intervals; AVA II, Advance vessel analysis version 2; HU, Hounsfield units.

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Introduction

The causal relationship between renal artery stenosis (RAS) and some cases of hypertension (HT) has been firmly established for several years. Despite the persisting controversy regarding the benefit of angioplasty for > 50% stenosis in atheromatous lesion, a search for RAS is recommended in patients suspected of reno-vascular HT or acute deterioration of renal function. Based on recent guidelines, either Doppler ultrasonography, computed tomography angiography or magnetic resonance angiography can be proposed as a screening test to establish the diagnosis of RAS [1–3]. Different authors have addressed the performance of CTA in the diagnosis of RAS, and in 2001, a meta-analysis by Vasbinder et al. [4] demonstrated satisfactory diagnosis accuracy supporting these guidelines.

In the Dutch RADISH trial [5], the unique largest prospective study published to date, 356 patients suspected of renal vascular hypertension were evaluated with computed tomography angiography, MRA, and compared to digital subtraction angiography (DSA), with the latter used as the reference standard [5]. They found that computed tomography angiography had an overall sensitivity of only 69%, with a specificity of 91% in a population where a prevalence of RAS was 20%. However, in this study, the vast majority of examinations were performed with a single-detector-row CT at 2.5- to 3.0-mm collimation.

Since the introduction of the multi-detector computed tomography, the diagnostic accuracy of computed tomography angiography for the diagnosis of RAS with the help of automatic arteries segmentation software has never been studied. One may hypothesize, however, that the technological progress allowed by the use of sub-millimetric thickness, high acquisition speed and high isotropic resolution, and post-processing imaging workstations equipped with arterial segmentation software, have increased both the sensibility (Se) and specificity (Sp) of these tests.

We undertook this retrospective cohort study to assess the accuracy of computed tomography angiography using state of the art multi-detector computed tomography unit and post-processing software. The aim of our study was to compare the diagnostic performance of multi-detector computed tomography angiography (MDCTA) versus renal DSA in the detection of RAS in patients suspected of reno-vascular HT.

Patient population and methods

Because of a retrospective data analysis, and in accordance to our national law, the Institutional Review Board approval was waived. The design of this work was performed in accordance with the recommendations of the Standards for Reporting of Diagnostic Accuracy initiative [6].

Study design

Between January 2005 and January 2010, all consecutive abdominal MDCTA and renal DSA of patients presenting reno-vascular hypertension available on our electronic patient record (EPR) were retrospectively reviewed at our institution. Only patient fulfilling the exclusion and inclusion

criteria were selected (Boxed text 1). All previous reports and patient data information were blinded to readers involved in the present study before imaging reanalysis. Because the most frequent clinical problem of renal artery stenosis are those related to atheromatous disease, we excluded fibro-dysplasia stenosis, radiation-induced stenosis, Takayasu's disease, vasculitis and surgical graft and patients with a renal stent in place. In addition, to assess the accuracy of MDCTA against arteriography, only cases in which an appropriate technique of image acquisition had been used within a short period of time (i.e. less than 6 months) were selected.

All renal arteriography were performed, using a Siemens Multistar system (Siemens AG, Medical Solutions, Erlangen, Germany), with a 5F pigtail catheter, using 30 mL of iobitridol (Xenetix® 350 Guerbet, Roissy France) contrast material, injected in 17 mL/s global, or 10 mL of contrast material in 10 mL/s for selective injections. Total contrast load to patients was approximately 60 mL. Selective arteriography was performed, using a 5F Shepherd hook catheter only in cases where the global angiogram was not able to depict appropriately the stenosis. The images were acquired at 3/s over a ≤ 30 cm field using both anterior posterior and 30° left anterior oblique projections. CTA protocol is described in Table 1.

During this period, 1078 patients had undergone both MDCTA and renal arteriography, of which 92 fulfilled the study inclusion/exclusion criteria as listed in Boxed text 1.

Image interpretation and analyses

All selected radiological records were transferred and anonymized from the EPR onto an ADW 4.4 image processing workstation (General Electric Healthcare, Waukesha, WI) in a DICOM format. To ensure that all readers would analyze the

Boxed text 1 Study inclusion and exclusion criteria.

Inclusion

- Clinical suspicion of reno-vascular HT
- Renal arteriography performed according to the protocol
- MDCTA performed according to the protocol (Table 2)
- MDCTA ≤ 6 months before arteriography
- Atheromatous stenosis

Exclusion

- Age < 20 years
- Pregnancy
- Non-atheromatous renal artery stenosis
- Surgical bypass graft
- Renal artery stent
- Images unavailable
- Poor technical quality of arteriography
- Poor technical quality of MDCTA according MDCTA setting (Table 2)
- Arterial attenuation < 250 UH*

*Arterial attenuation was measured in the aorta just upon renal artery ostia.

Table 1 Settings of computed tomographic angiographic systems tested in this study.

	Somatom 4 Siemens	VCT Light speed GE
Slice thickness, mm	4 × 1.25	64 × 0.625
Reconstruction increments	1.25	0.625
Pitch	1.0	0.984
Voltage at the tube terminal (Kv)	≥ 120	≥ 120
mAmpere/s	500 mAs self adapted	450 mAs self adapted
Matrix	512 × 512	512 × 512
Filter	B30f	Abdominal
Iodinated contrast material	80 mL Xenetix® 350	80 mL Xenetix® 350
Detection of contrast material bolus	Bolus care system: > 200 UH	Smart Prep system: > 200 UH
Field of view	380	360
Acquisition time, s	12.0	7.3

same arteries and segments, the study coordinator labeled on DSA and MCTA all arteries before to start the study.

Analysis of arteriographic images

Renal arteriography analysis was performed by one senior interventional radiologist (9 years experience). He classified in all renal arteries the lesion location (ostial, truncular and bifurcation) and their percentage diameter stenosis (defined as the ratio between the lesion and the reference vessel internal diameters). The reference vessel diameter was measured distally to the stenosis, beyond the area of post-stenotic dilatation, and proximally to the first bifurcation of the vessel under examination. The results of DSA were considered as the gold standard for our study.

Analysis of multi-detector CTA images

The images were interpreted by three readers: two senior radiologists (7 and 9 years of experience in vascular diagnostic radiology) with expertise in the use of post-imaging workstations and software, and one technician, with expertise limited to the use of automated post-imaging workstations and software. All analytical method was timed.

The first reader (senior radiologist) analyzed the MDCTA, using original thin section axial image and post-processing MIP (3 mm thickness) and MPR (1 mm thickness) images. After the detection of the vascular anatomy on a MIP view, the stenosis and the reference vessel diameters were both measured on an MPR view perpendicular to the artery's main axis on 0.625- or 1.25-mm sections. The diameters were manually measured using identical viewing windows (WW = 420; WL = 120) for all patients.

The second and the third reader use advance vessel analysis version 2 (AVA II) (GE Healthcare Waukesha, WI) for image interpretation. AVA II is an automatic artery segmentation software, that could be used with or without readers editing.

The second reader (technician) used the AVA II without any personal editing. AVA II software comprised the following automated steps: Upon the software's command, a first caliper was placed in the aortic lumen, and a second in the first bifurcation branch of the renal artery (Fig. 1). The artery is then automatically tracked by AVA II and the stenosis is measured automatically by the software, using as a reference the vessel diameter distal to the stenosis, beyond the area of post-stenotic dilatation. After three unsuccessful attempts at automated analysis, the observer was authorized to proceed with the placement of three fiducial points, allowing

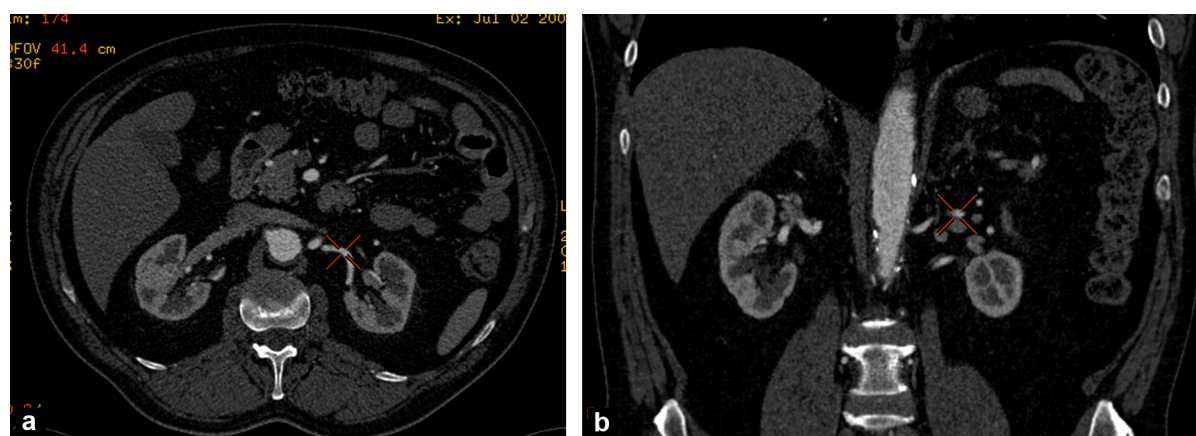


Figure 1. Sixty-eight-year-old man with reno-vascular hypertension, referred to renal arteries CTA. This patient present one right renal artery and two left renal artery. Two calipers on transverse (a) and sagittal (a) views are placed along the lower renal artery. The arterial segmentation is performed from these fiducial points, from the aorta toward the distal artery.

tracking of the artery. This reading method allows an evaluation of the software's performance in itself, by assessing:

- its efficacy in detecting the vascular network;
- the accuracy of the measurements.

In the event of unsuccessful automatic arterial tracking by the software, the observer:

- repeated the procedure three times;
- reported the cause of failure and means of circumvention.

The third reader (senior radiologist) analyzed the MDCTA, using AVA II, and applying all the modifications needed to reach a result judged as satisfactory such as correction

of center line tracking errors or diameter tracking errors (Figs. 1 and 2).

In summary, the difference between the second and the third reader was that the second was not allowed to do any manual correction in order to assess the autonomy of the software while the third used AVA II corrected by human intervention (in order to assess the combined result of the intervention of the radiologist based on the software help).

Statistical analysis

Because of a < 3.0 mm diameter or ectopic site of their origin, some arteries were not suitable for DSA. Consequently,

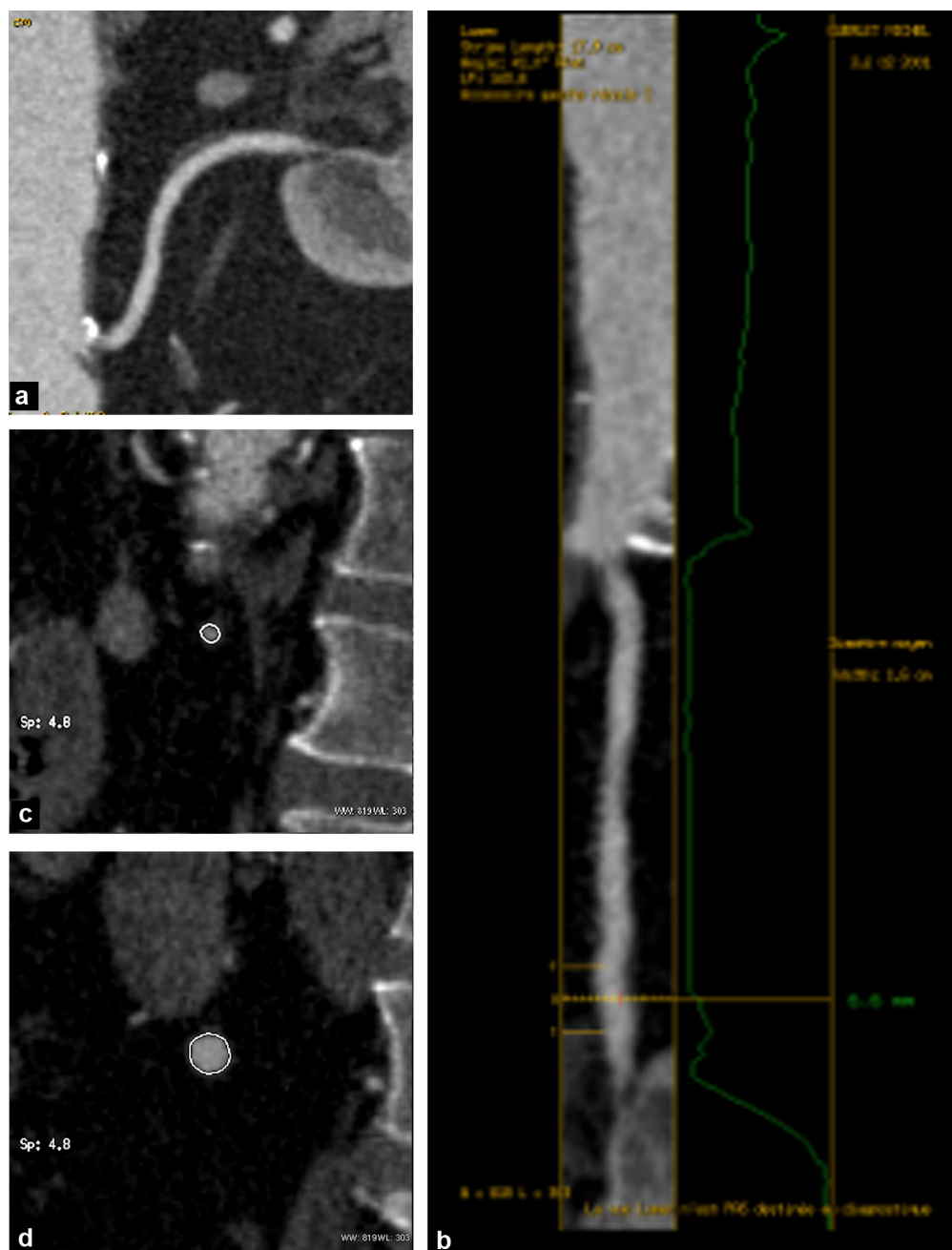


Figure 2. Same patient as Fig. 1. From the tracing obtained, a curve multiplanar projection shows the arterial anatomy (a), enabling a measurement of stenosis diameter in a planar projection (b), or in a orthogonal MRP projection (c) and reference diameter (d). In this case, the ostial stenosis was 80%.

we calculated the Sp, Se, predictive values and likelihood ratios (LR), including uninterpretable observations in a 6-cell matrix, as described by Simel et al. [7]. The data were analyzed separately with respect to the number of patients and to the number of renal arteries.

When analyzed with respect to the number of patients, 95% confidence intervals (CI) of proportions were calculated using the Wilson method [8] and CI of LR were calculated, using the "score test" method [9].

When analyzed with respect to the number of renal arteries, we treated patients as clusters and the renal arteries as diagnostic units within each cluster. Therefore, the calculation of CI for proportions was based on a ratio estimator for the variance of clustered binary data, which takes intraclass correlations into account [10]. Percentile CI of LR was calculated using bootstrap resampling [11]. We compared the Se and Sp of MDCTA with AVA II with that of MDCTA with MPR, using McNemar's test for the patient-based analyses, and Durkalski's method, which adjusts for multiple units within a cluster, for the artery-based analyses [12].

The statistical analyses were performed using the SAS v9.1 software (SAS Institute, Cary, NC). A *P* value < 0.05 was considered statistically significant.

Results

The patients' flow, from their screening to their inclusion in the study, and the outcomes of MDCTA versus renal arteriographic analyses, are shown on Fig. 3. The most frequent reason for exclusion of a patient was a too long delay between MDCTA and DSA. We also faced 190 patients in which arterial opacification was not sufficient on MDCTA [< 250 Hounsfield Units (HU)].

Among the 92 patients included in the study, 56 underwent 4-channel Somatom (Siemens) MDCTA and 36

underwent MDCTA on a 64-channel VCT (General Electric) unit. The baseline demographic and clinical characteristics, and radiological observations made in the 92 patients are shown in Table 2.

Results of renal arteriography analysis

A total of 235 renal arteries were analyzed, including 92 left main, 95 right main, 21 left accessory, 27 right accessory (eight arteries could not be identified by the reader because of no opacified ectopic take off). This accounted for a mean of 2.5 arteries per patient, (2 main and 0.5 accessory), 48 arteries presented with a $> 50\%$ stenosis, [ostial in 44 (92%) and truncular in four (8%)].

Results of multi-detector CTA readings

Among 243 arteries analyzed by three readers, 48 stenosis were classified $> 50\%$ by the three readers. Table 3 shows the Se and Sp and 95% CI of each analytical method. Those results were calculated as function of the number of arteries and patients, respectively.

The best method appears to be the reader 3 approach: use of AVA II with manual corrections. This method yields a

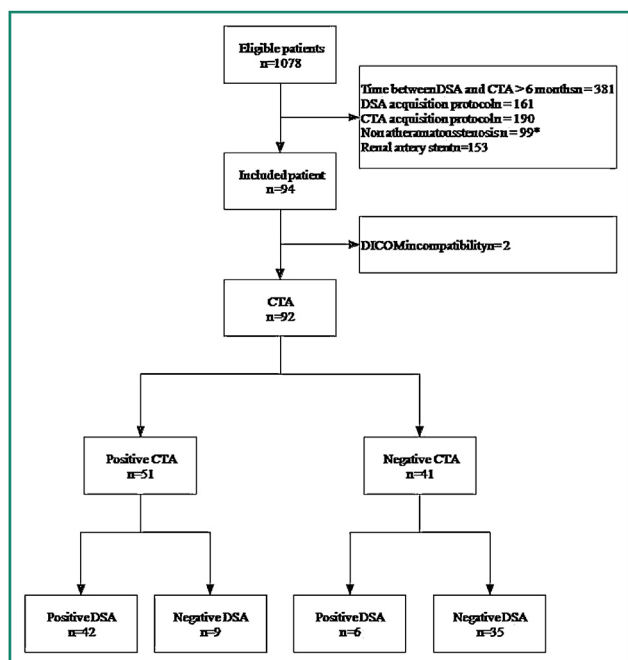


Figure 3. Patient flow-chart.

Table 2 Patients (*n* = 92) demographic and clinical characteristics at base line.

Age, year	71 ± 17 (41–92)
Men/women	50 (54%)/42 (46%)
Smoking history	33 (34%)
Baseline systemic pressure, mmHg	
Systolic	178 ± 18 (115–198)
Diastolic	110 ± 15 (70–130)
Duration of hypertension, y	4 ± 12 (0–35)
Body mass index	26 ± 7 (16–51)
Plasma serum creatinine, μmol/dL	111 ± 55 (75–150)
Computed tomographic angiography	
Siemens SOMATOM	56 (60%)
General Electric LightSpeed™ VCT	36 (40%)
Left kidney	
Cortical index, mm	5.3 ± 1.4 (5–6)
Size, mm	105 ± 14.5 (96–115)
Right kidney	
Cortical index, mm	6.5 ± 8.3 (5–6)
Size, mm	104 ± 12 (97–112)
Ectopic kidney	2 (2%)
Abdominal aortic aneurysm	2 (2%)

Unless specified otherwise, values are means ± SD (range), or numbers (%) of observations.

Table 3 Diagnostic value of computed tomographic angiography in the detection of a > 50% stenosis; analysis per arteries and per patients.

	Reader 1: MPR/MIP	Reader 2: Automated AVA II	<i>P</i> ^a	Reader 3: Manual AVA II	<i>P</i> ^b
Per artery analysis					
Sensitivity	74 [63 to 86]	44 [31 to 57]	0.001	84 [74 to 95]	0.02
Specificity	90 [86 to 95]	90 [86 to 95]	0.58	94 [86 to 95]	0.75
Positive predictive value	71 [60 to 82]	60 [46 to 73]		74 [64 to 84]	
Negative predictive value	91 [87 to 96]	83 [78 to 89]		95 [91 to 99]	
Positive likelihood ratio	7.5 [4.9 to 13.1]	4.5 [2.7 to 8.4]		8.6 [5.7 to 15.2]	
Negative likelihood ratio	0.3 [0.2 to 0.4]	0.6 [0.5 to 0.8]		0.2 [0.1 to 0.3]	
Per patient analysis					
Sensitivity	88 [75 to 94]	58 [44 to 71]	0.004	96 [86 to 99]	0.22
Specificity	80 [66 to 89]	80 [66 to 89]	1.00	90 [68 to 91]	1.00
Negative predictive value	82 [70 to 90]	76 [60 to 87]		85 [73 to 92]	
Positive predictive value	85 [72 to 93]	64 [50 to 75]		95 [83 to 99]	
Positive likelihood ratio	4.3 [2.5 to 7.9]	2.9 [1.6 to 5.4]		5.3 [3.0 to 10.0]	
Negative likelihood ratio	0.2 [0.1 to 0.3]	0.5 [0.4 to 0.7]		0.05 [0.01 to 0.2]	
CTA: computed tomography angiography; AVA II: advance vessel analysis version 2.					
^a <i>P</i> value associated to the test comparing the sensitivity/specificity of CTA with automated AVA II to CTA with MPR/MIP.					
^b <i>P</i> value associated to the test comparing the sensitivity/specificity of CTA with manual AVA II to CTA with MPR/MIP0.					

Se of 84%, Sp of 94%, and positive predictive value of 74% and negative predictive value of 95%. When one considers the per-patient analysis these figures are even higher.

In addition, changes in the arterial segmentation trace were made in 32 analyses (35%) by the second observer; versus 44 analyses (49%) by the third observer. Furthermore, the third observer changed the position of the central lines in 29 analyses (32%), and corrected the vessel diameters in 58 (64%) analyses. The causes of unsuccessful tracking during AVA II were tortuous vessel two cases (2%), stenosis four vessels (4.5%), venous return 10 vessels (11%), small artery one (1%), calcified ostium 7 (8%), insufficient contrast three (3%), vascular overlap seven (8%), metal artifact one (1%). They are illustrated on Figs. 4 and 5.

The mean duration of the MDCTA analyses by the three methods are $8.5 \text{ min} \pm 3.4$ (3–20) for the first reader, $3.5 \text{ min} \pm 2.2$ (1–12) for the second reader, and $7.6 \text{ min} \pm 4.3$ (2–30) for the third. All differences between the readers in term of analysis duration are significant ($P < 0.001$). No significant difference was observed between the 4- and the 64-channel MDCTA.

The median time interval between renal artery MDCTA and renal angiograms was 95 days (range 1–178). The mean renal dimension was $105 \pm 13 \text{ mM}$, and mean cortical index $6.0 \pm 1.2 \text{ mm}$. An abdominal aortic aneurysm, between (42 mM and 58 mM in diameter), was incidentally discovered in two patients (2.1%), and two patients (2/1%) presented with ectopic kidneys, including one left and one right pelvic kidneys (Table 2).

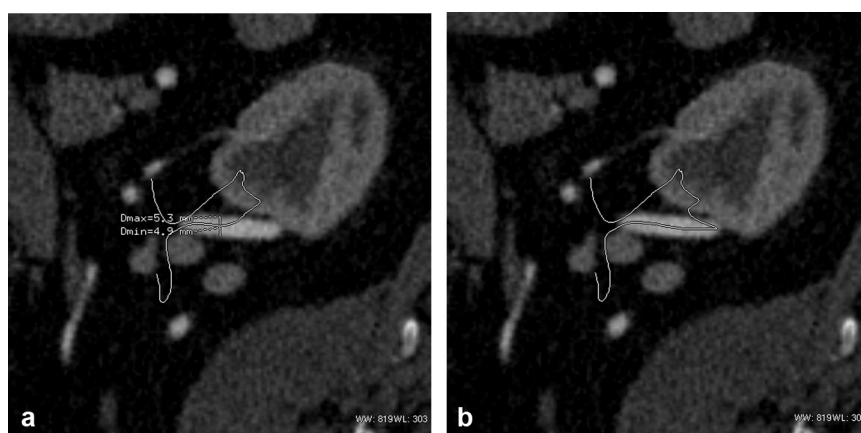


Figure 4. Same patient as Fig. 1. Common tracking error. The track of the artery was not properly recognized by the segmentation algorithm (a). This requires manual correction (b).

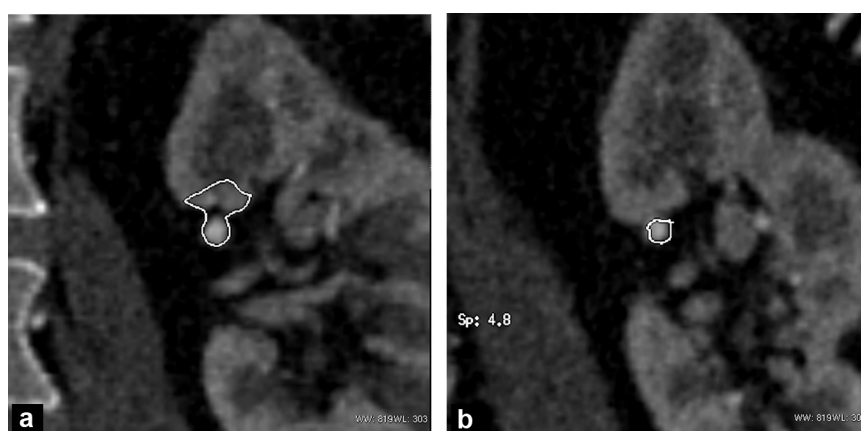


Figure 5. Same patient as Fig. 1. Common erroneous measurement of arterial diameter for reasons similar to those identified on Fig. 4 (a), and its manual correction (b).

Discussion

The main finding of our retrospective study was that using the third reader approach we observed a Se/Sp of 84%/94% per artery in the detection of atheromatous renal artery stenosis.

All the results reported in the literature relates to per artery analysis. Vassbinder et al. [5] (in the Dutch RADISH trial) in 2004 report a lower Se/Sp of 64%/92% and others reported 94–100% Se and 92–99% Sp [5,13–19]. Comparison of all studies is difficult for methodological as well as statistical reasons. For example, in Vassbinder et al. [5] trial and only for purely statistical reasons, more than >300 patients' sample size would have been needed to confirm a statistically significant 5% difference in Se and Sp. We can still hypothesize different explanation to account for the difference in published results. First the technical improvement using modern MDCTA units: the slice thickness (0.625 or 1.2 mm) is lower and spatial resolution is increased. In the work of Vassbinder et al., slice thickness was 2.5 or 3 mm. Second, the prevalence of disease was 50% in our study versus >70% in most other studies, except in Vassbinder et al. [5] trial (prevalence was 20%). In addition, the sample sizes of earlier studies were smaller than ours.

This may modify the results of sensitivity and specificity in an unpredictable manner.

Third, and this is probably one important feature, was the fact that our study is the only one using the recommended Standards for Reporting of Diagnostic Accuracy initiative [6]. This approach was designed with the aim to reduce the methodological bias that may modify the results. Despite the patient work flow (as shown on Fig. 3) demonstrates that a high number of patients were excluded from the study for various reasons, we were able to analyze a high number of patients as compared to most previously published series [13–16,18,19].

The role of post-processing technique is also of importance and we sought to achieve a comprehensive approach to this problem, which may significantly influence the daily practice in term of quality of the results as well as post-processing time. The use of the automated arterial segmentation software combined with human verifications (third observer) increased dramatically the Se per artery as well as per patient, compared with the automated analysis only (second observer), though Sp was similar. The results of the third reading method were also superior to those of the first (MPR/MIP).

Despite the absence of published formal comparison of these methods, it is well known that the MPR/MIP analytical method is associated with reliable results and high inter-observer reproducibility [18,20]. The Se of the automated AVA II segmentation software alone, per patient as well as per artery, was lower (44 and 58%, respectively) than that observed with the MPR/MIP method (74 and 88%, respectively), though the Sp was similar. These observations are consistent with previous experimental studies, which found a high Sp of this software, reflecting the precision of the measurements [21,22]. The lower Se can be attributed to tracking deficiencies, due to vascular calcifications, venous return and vascular overlap. This is also consistent with our findings because failure of AVA II automatic processing was always related to one of these conditions. Indeed, we found that the best approach was to use AVA II automatic software followed by manual corrections, allowing significantly better results than using MPR/MIP or when AVA II was performed without radiological expertise. In addition, the third reading approach (manual AVA II) was shorter than when reading was done manually from MPR and MIP views. We found also a very high concordance in the number of arteries per patient both on MDCTA and DSA, we consider this a direct consequence of our pre-specified protocol in which the coordinator of the study previously reviewed all images and pointed the arteries to be studied.

Clinical applicability of our results may be further discussed. The importance of the detection of RAS lies in the potential finding of a curable form of hypertension (5% of hypertensive patients). Furthermore, the presence of RAS is an independent prognostic risk factor of cardiovascular complications. The clinical consequence of such finding can be renal artery stenting or watchful follow-up according to the patient clinical condition. When using a screening method to rule-out renal artery stenosis, one looks for a reliable non invasive method that can be applied to a large collective of patients, and MDCTA is the preferred screening method in our institution as well as in several others. The referring clinicians is more concerned by the in-patients analysis because the question is whether a patient has at least a stenosis > 50% in any one of his renal arteries. We have shown a 96/90% Se/Sp for stenosis detection when the results were assessed on a per patient basis. Moreover, we found that the negative predictive value was 95% (per patient analysis), which re-enforces the validity of the test.

In this retrospective study based on clinical practice, a proportion of patients were included who underwent renal arteriography in pursuance of observations made in a previously performed MDCTA. This could represent a bias in the incidence of stenosis in this population of patients but not in the image interpretation. Likewise, no statistically significant difference was observed in the Se and Sp of 4 slices versus 64 slices MDCTA although it may exist. One other limitation is directly linked to arterial software. Arterial segmentation software works with a pixel-by-pixel analysis based on a radial function analysis. This radial function is defined by propagation or restriction front wave. Wave forces are applied depending on the pixel's value. In other words, only contiguous anatomical structures with high-density level could be determined and selected as arterial network. A high enhancement level (> 250 HU) is therefore

recommended to perform the segmentation of a vascular structure. To overcome segmentation failure related to low enhancement level, we chose 250 HU as the cut-off value. In our study, a renal artery density above 250 HU could not be obtained for 190 of our patients. Such results underline the need to optimized injection and acquisition protocols when assessing renal artery disease with CTA. Despite these limitations, and especially because we followed the recommended Standards for Reporting of Diagnostic Accuracy initiative in the design of the study, we believe these results are of interest.

Conclusion

In summary, our study confirms that MDCTA images analyzed using the AVA II software edited by the radiologist allows to depict atheromatous > 50% RAS with a Se/Sp of 96%/90% (per patient) and a positive/negative value of 85%/95% with the need for 7.6 min of reading time per patient.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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